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Survival predictors in patients treated with a molecular adsorbent recirculating system

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Abstract

AIM: To identify prognostic factors for survival in patients with liver failure treated with a molecular adsorbent recirculating system (MARS).

METHODS: MARS is a liver-assisting device that has been used in the treatment of liver failure to enable native liver recovery, and as a bridge to liver transplantation (LTX). We analyzed the 1-year outcomes of 188 patients treated with MARS, from 2001 to 2007, in an intensive care unit specializing in liver disease. Demographic, clinical and laboratory parameters were recorded before and after each treatment. One-year survival and the number of LTXs were recorded. Logistic regression analysis was performed to determine factors predicting survival.

RESULTS: The study included 113 patients with acute liver failure (ALF), 62 with acute-on-chronic liver failure (AOCLF), 11 with graft failure (GF), and six with miscellaneous liver failure. LTX was performed for 29% of patients with ALF, 18% with AOCLF and 55% with GF. The overall 1-year survival rate was 74% for ALF, 27% for AOCLF, and 73% for GF. The poorest survival rate, 6%, was noted in non-transplanted patients with alcohol-related AOCLF and cirrhosis, whereas, patients with enlarged and steatotic liver had 55% survival. The etiology of liver failure was the most important predictor of survival ($P < 0.0001$). Other prognostic factors were encephalopathy ($P = 0.001$) in paracetamol-related ALF, coagulation factors ($P = 0.049$) and encephalopathy ($P = 0.064$) in non-paracetamol-related toxic ALF, and alanine aminotransferase ($P = 0.013$) and factor V levels ($P = 0.022$) in ALF of unknown etiology.

CONCLUSION: The etiology of liver disease was the most important prognostic factor. MARS treatment appears to be ineffective in AOCLF with end-stage cirrhosis without an LTX option.

Key words: Molecular adsorbent recirculating system; Prognostic factors; Acute liver failure; Acute-on-chronic liver failure; Liver transplantation

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INTRODUCTION

Since its introduction in 1993, molecular adsorbent recirculating system (MARS) albumin dialysis[1,2] has been a subject of research, with the hope of using it to treat effectively patients with rapidly failing liver function. Even though MARS treatment cannot fully compensate for the synthetic and metabolic functions of a normal liver, it has been used as a bridging treatment to sustain the patient until a suitable graft becomes available, or the native liver recovers. MARS treatment has also been used for patients who have a contraindication to transplantation or when a suitable organ is not available.

While the effect of MARS treatment on patient outcome, and laboratory and clinical parameters has been investigated widely in various uncontrolled case series, only a handful of randomized studies have been published[5-9]. Thus, we are still searching to identify which patients are most likely to benefit from this treatment, and to determine whether MARS treatment does in fact improve survival in patients with liver failure. It is crucial to identify not only those patients who have a good possibility of benefiting from MARS treatment, but also those for whom MARS treatment is a futile tool that serves only to prolong suffering when death is imminent.

The aim of this prospective observational study was to identify prognostic factors associated with survival in MARS-treated patients with life-threatening liver failure.

MATERIALS AND METHODS

This was an uncontrolled, prospective, single-center, observational study of 188 consecutive patients who underwent MARS treatment in a liver-disease-specialized intensive care unit (ICU) from May 2001 to March 2007. Four patients were treated before LTX, and then later on after LTX because of graft failure. All patients were categorized into four main groups according to the etiology of liver failure: acute liver failure and injury (ALF), acute-on-chronic liver failure (AOCLF), liver graft failure (GF), or liver failure of miscellaneous etiology. For the final analysis of results, these groups were further divided into subgroups according to specific etiology (Figure 1). Our tertiary liver-disease-specialized ICU is the only transplantation center in Finland.

Patients included in the ALF group required ICU admission and had rapid development of hepatic synthetic dysfunction[10], with or without encephalopathy, and no previous history of liver disease. AOCLF was defined as previously well-compensated chronic liver disease in which an acute decompensation of liver function developed rapidly, as a result of various secondary causes[11]. Graft failure included early (primary dysfunction or non-functioning graft) and late (primarily chronic rejection) dysfunction. The miscellaneous etiologies group contained patients with acute hemorrhagic pancreatitis with ALF, ischemic injury to the liver following myocardial infarction, multiple trauma including injury to the liver, and post-liver resection hepatic failure.

Monitoring and standard medical therapy

All patients received the same standard medical therapy. Blood pressure was monitored *via* arterial and central venous catheters; a Swan-Gantz catheter was used if necessary. All potentially nephro- and hepatotoxic medications were discontinued. Mean arterial pressure was maintained above 65 mmHg with fluid resuscitation and vasoactive medication (primarily noradrenaline infusion). Surveillance for infection and prophylactic antibacterial and antifungal therapy was administered. The level of consciousness was monitored closely and sedatives were avoided in non-intubated patients. If the grade of hepatic encephalopathy was $\geqslant$ 3 according to the West Haven

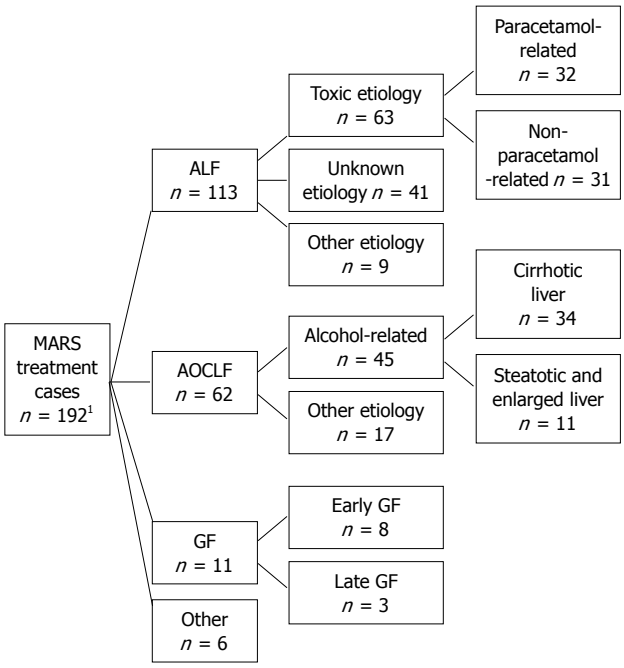

Figure 1 Distribution of liver failure etiologies in MARS-treated patients. [1]192 MARS treatment cases and 188 patients were included in this study. Four patients were treated at two different time points, first due to the primary liver failure, and second for graft failure following LTX.

criteria[12], the patient was usually sedated, intubated, and mechanically ventilated. A standard regimen of lactulose and proton pump inhibitors was used, and the target blood glucose level was normoglycemia, which was maintained with glucose and insulin infusion. *N*-acetylcysteine was used when necessary. Enteral nutrition was employed if possible. Urinary output was monitored and fluid resuscitation with furosemide infusion was used if necessary. Laboratory assessment of coagulation parameters was performed daily and clotting abnormalities were corrected only in cases of active bleeding, or an invasive procedure. Specific antidotes and drug therapies such as silibinin[13] and corticosteroids were used if deemed necessary.

MARS treatment initiation criteria

The criteria for initiating MARS treatment and treatment protocols are summarized in Table 1. In some patients, MARS treatment was commenced in the absence of encephalopathy, particularly in ALF patients who had ingested a lethal amount of toxin or if laboratory parameters indicated progressive liver failure despite the best possible standard medical therapy. As a general rule, we treated only the first exacerbation of chronic alcoholic liver disease.

In the MARS apparatus, the flow rate was 150 mL/min in the blood and albumin circuit and 500 mL/min in the dialysis circuit with bicarbonate buffered dialysate. Ultrafiltration was adjusted to control intravascular volume balance. Anticoagulation was used if permitted by the coagulation status and platelet count of the patient; dalteparin or epoprostenol were used most often. A detailed description of the operational systems of the MARS machine can be found in our previous study[14].

Table 1 Indications for MARS and treatment protocols

Etiology	MARS treatment initiation criteria	Treatment protocol
ALF	Rapid deterioration of hepatic synthetic function and clinical condition despite standard medical therapy and (one of the following criteria)	Twenty-two hours sessions daily until the native liver recovers
	Ingestion of a lethal dose of a known hepatotoxin (mushroom, paracetamol, iron, *etc*)	A suitable transplant organ is found
	Patient fulfills the criteria for highly urgent Ltx	Irreversible organ damage occurs
AOCLF	Rapid deterioration of hepatic synthetic function and clinical condition despite standard medical therapy and (two of the following criteria)	Eight hours sessions based on the daily assessment of the surgeon and anesthesiologist until the patient's clinical condition improves
	Hyperbilirubinemia, bil > 400 μmol/L	A suitable transplant organ is found
	Hepatorenal syndrome type 1	Irreversible organ damage occurs
	Progressive hepatic encephalopathy (grade ⩾ 2)	
GF	No set criteria; depends on the assessment of the transplant surgeon and anesthesiologist	No set protocol; based on the daily assessment of the surgeon and anesthesiologist

ALF: Acute liver failure; AOCLF: Acute-on-chronic liver failure; GF: Graft failure.

Table 2 Demographic, clinical, and treatment data at the beginning of MARS treatment

Characteristic	All patients	ALF			AOCLF		Graft failure
		Toxic	Unknown cause	Other	Alcohol-related	Other	
Number of patients	192	63	41	9	45	17	11
Age, years	49 (14-81)	41 (14-81)	51 (19-68)	43 (32-58)	52 (30-71)	54 (16-75)	47 (18-62)
Sex, % male (*n*)	48 (93)	48 (30)	32 (13)	33 (3)	69 (31)	47 (8)	36 (4)
Body mass index, kg/m^2	26 (17-56)	24 (17-40)	28 (19-37)	28 (23-34)	27 (18-46)	27 (20-56)	27 (19-56)
MARS sessions/patient	2 (1-13)	2 (1-8)	3 (1-12)	3 (1-9)	2 (1-13)	2 (1-9)	2 (1-4)
Duration of MARS session, h	16.5 (4-22.5)	15.0 (5.5-22)	16.8 (4-22)	16.0 (6.4-22)	20.1 (7.8-22)	18.3 (4.5-22.5)	17.5 (9.5-22)
Mechanically ventilation used, % (*n*)	36 (69)	29 (18)	34 (14)	56 (5)	29 (13)	41 (7)	73 (8)
Vasoactive-medications used, % (*n*)	43 (82)	33 (21)	27 (11)	33 (3)	47 (21)	82 (14)	63 (7)
Renal insufficiency, % (*n*)	49 (94)	33 (21)	37 (15)	44 (4)	60 (27)	76 (13)	73 (8)
MELD score	32 (5-52)	27 (5-48)	32 (23-50)	27 (23-46)	39 (17-52)	36 (27-44)	26 (20-47)
Mean encephalopathy grade before treatment (± SD)	1.8 (1.5)	1.6 (1.6)	2.0 (1.4)	2.4 (1.7)	1.5 (1.4)	1.9 (1.6)	2.0 (1.9)
Mean encephalopathy grade after treatment (± SD)	1.4 (1.6)	1.4 (1.7)	1.5 (1.7)	1.4 (1.6)	1.1 (1.5)	1.9 (1.8)	1.3 (1.7)
P	< 0.001	NS	0.05	0.04	0.02	NS	0.059

All demographic values are expressed as median (range) or percentage of patients (number of patients). Encephalopathy grades are expressed as mean ± SD). NS: Non-significant.

Measurements and data collection

For all MARS-treated patients, detailed information regarding the patient and treatment session was collected prospectively on a specially designed data collection sheet. Demographic data and clinical parameters were recorded at the beginning and end of each treatment. Baseline measurement was performed at the beginning of the first MARS session. The endpoint was the end of the last MARS session, death, or LTX. At both time points, blood samples were analyzed for cell counts, coagulation factor levels, plasma levels of liver enzymes, bilirubin, ammonium ion, urea, creatinine, blood gases, and electrolytes. The value furthest from the normal range of each measured variable during treatment was not included in the present analysis. The model for end-stage liver disease (MELD) score was calculated according to the standard formula by the United Network for Organ Sharing (UNOS)[15-17] at ICU admission. Survival at 1-year and need for LTX were recorded.

Statistical analysis

All data were analyzed with SPSS for Windows version 15.0 (SPSS, Chicago, IL, USA). The Wilcoxon signed rank test was used for repeated scale measurements before and after treatment within groups. The Mann-Whitney *U* test was applied when scale measurements were compared between groups. The Pearson χ^2 and Fisher exact tests were used to compare outcomes and binominal results between groups. $P \leqslant 0.05$ was considered statistically significant.

Stepwise binary logistic regression analysis was performed to determine factors predicting survival in each etiological subgroup. Variables analyzed included all collected demographic, clinical and treatment-related variables (Table 2) and all laboratory parameters at baseline (Table 3). Missing laboratory values were replaced with the median value of that laboratory result in all patients. The median was used instead of the mean because of the skewed distribution of most results. Special attention was given to variables that changed during MARS treatment and parameters that differed between transplant-free survivors and non-survivors/transplanted patients. The odds ratio (OR) and 95% confidence interval (CI) for each predictive variable were calculated. The best combination

Table 3 Changes in laboratory parameters during MARS treatment in different liver failure subgroups

	Before MARS	After MARS	Percent change	*P*	Before MARS	After MARS	Percent change	*P*	Before MARS	After MARS	Percent change	*P*
	Toxic ALF (*n* = 63)				Unknown-cause ALF (*n* = 41)				Other ALF (*n* = 9)			
Hemoglobin g/L	110 (77-170)	100 (59-136)	-9	< 0.001	110 (74-146)	98 (71-134)	-11	0.001	98 (80-131)	88 (82-120)	-10	NS
Leucocytes 10^9/L	8.6 (1.0-29.2)	8.7 (2.4-33.9)	1	NS	8.9 (2.8-21.9)	8.4 (2.9-42.5)	-6	NS	7.6 (2.6-41)	11.4 (1.7-30.6)	50	NS
Platelets 10^9/L	130 (11-438)	80 (9-349)	-38	< 0.001	140 (48-511)	74 (25-327)	-47	< 0.001	97 (37-248)	85 (19-184)	-12	0.04
CRP g/L	9 (5-157)	15 (5-186)	67	< 0.001	8 (5-120)	10 (5-142)	25	0.006	30 (5-331)	33 (5-148)	10	NS
Creatinine μmol/L	79 (35-1318)	51 (17-585)	-35	< 0.001	84 (36-572)	54 (17-337)	-36	< 0.001	85 (57-567)	53 (23-149)	-38	0.02
Urea mmol/L	4.8 (0.8-31.2)	1.7 (0.2-11.7)	-65	< 0.001	6.3 (1.0-25.6)	1.8 (0.8-58)	-71	< 0.001	12.0 (4.2-29.3)	4.3 (1.0-6.7)	-64	0.01
NH_4-ion μmol/L	75 (18-512)	55 (3.5-258)	-26	< 0.001	75 (24-244)	56 (20-309)	-25	0.006	81 (8-317)	45 (17-176)	-45	NS
Bilirubin μmol/L	84 (4-761)	97 (6-355)	15	0.05	472 (35-725)	301 (10-570)	-36	< 0.001	372 (62-694)	190 (94-348)	-49	NS
AST U/L	842 (15-24360)	282 (15-5240)	-67	< 0.001	427 (50-18140)	183 (19-4080)	-57	< 0.001	600 (37-12640)	83 (43-2227)	-86	NS
ALT U/L	1120 (11-12500)	565 (5-9970)	-50	< 0.001	550 (71-11946)	174 (33-7790)	-68	< 0.001	217 (22-6710)	171 (21-1321)	-21	0.04
γ-GT U/L	72 (8-2139)	55 (9-1279)	-24	0.01	106 (20-503)	49 (5-238)	-54	< 0.001	157 (21-1422)	62 (22-1010)	-61	NS
FV %	33 (5-201)	51 (5-149)	55	0.07	33 (5-119)	23 (7-101)	-33	NS	55 (7-100)	53 (26-127)	-3	NS
AT3 %	44 (15-125)	41 (15-122)	-6	0.002	26 (15-78)	27 (15-68)	4	NS	32 (19-110)	33 (18-92)	3	NS
TT (%)	22 (6-80)	30 (6-112)	36	NS	17 (6-44)	18 (6-68)	3	NS	26.5 (6-53)	36 (16-52)	36	NS
INR	2.5 (1.1-7.7)	2 (1.0-9.9)	-20	NS	3.1 (1.5-9.9)	2.8 (1.5-10)	-10	NS	2.3 (1.4-5.5)	1.8 (1.4-3)	-22	NS
	Alcohol-related AOCLF (*n* = 45)				Other AOCLF (*n* = 17)				Graft failure (*n* = 11)			
Hemoglobin g/L	101 (59-129)	94 (75-123)	-7	0.01	96 (71-130)	91 (75-104)	-5	NS	96 (86-117)	99 (71-123)	3	NS
Leucocytes 10^9/L	17.2 (5-39.3)	16.7 (2.1-45.7)	-3	NS	10 (1.4-30.7)	5.7 (1.3-30)	-43	0.01	9.5 (1.7-14.9)	8.8 (2.1-20.8)	-7	NS
Platelets 10^9/L	129 (15-508)	83 (6-349)	-36	< 0.001	82 (27-238)	57 (19-215)	-30	0.004	81 (27-453)	83 (16-206)	2	NS
CRP g/L	32 (5-110)	38 (5-160)	19	NS	35 (5-67)	38 (5-110)	9	0.01	22 (6-172)	23 (9-64)	5	NS
Creatinine μmol/L	167 (49-686)	65 (20-216)	-61	< 0.001	210 (29-325)	52 (17-149)	-75	< 0.001	159 (39-301)	70 (22-121)	-56	0.003
Urea mmol/L	17.5 (1.8-56.5)	3.5 (0.7-18.3)	-80	< 0.001	16.9 (3.2-27.4)	3.1 (1.2-12.3)	-82	< 0.001	16.5 (6.0-32.3)	4.7 (1.3-10.0)	-72	0.004
NH_4-ion μmol/L	73 (12-311)	60 (23-144)	-18	0.05	89 (19-223)	62 (21-96)	-30	0.03	47 (17-177)	32 (25-69)	-32	NS
Bilirubin μmol/L	513 (17-840)	271 (14-499)	-47	< 0.001	481 (278-909)	283 (134-530)	-41	0.001	311 (107-720)	223 (74-348)	-28	0.009
AST U/L	156 (27-4540)	140 (13-1959)	-10	0.002	210 (31-1230)	144 (58-1222)	-31	0.03	321 (27-12560)	226 (53-87380)	-30	NS
ALT U/L	74 (9-2904)	69 (8-2480)	-7	< 0.001	100 (18-681)	85 (27-286)	-16	0.07	722 (38-9460)	4400 (48-25120)	509	NS
γ-GT U/L	198 (29-1086)	147 (19-810)	-26	< 0.001	69 (19-429)	61 (12-342)	-12	NS	180 (26-2385)	174 (34-1619)	-3	NS
FV %	53 (8-125)	46 (8-131)	-12	< 0.001	34 (7-124)	26 (8-124)	-24	0.005	79 (7-131)	77 (13-107)	-3	NS
AT3 %	34 (13-88)	29 (15-67)	-13	0.001	29 (15-100)	23 (15-100)	-21	0.01	54 (15-137)	56 (17-104)	-4	NS
TT (%)	22 (9-135)	17 (6-49)	-23	0.02	20 (6-96)	17 (6-73)	-15	NS	42 (8-139)	47 (20-113)	-12	NS
INR	2.4 (1.3-5.6)	2.9 (1.3-9.9)	21	0.03	2.4 (1-8.5)	2.9 (1.1-8.5)	21	0.01	1.5 (0.9-6.4)	1.5 (1.0-2.8)	0	NS

All laboratory values are expressed as median (range). NH_4-ion: Ammonium ion (normal range: 36-86 mmol/L); AST: Aspartate aminotransferase; γ-GT: gamma glutamyltransferase; FV: Coagulation factor Ⅴ (normal range: 80%-120%); AT3: Antithrombin Ⅲ (normal range 80%-120%); TT (%): Thrombin time (normal range, 70%-130%) (includes coagulation factors Ⅱ, Ⅶ, Ⅹ).

of significantly predictive variables was selected using the R^2 score and Hosmer-Lemeshow goodness of fit test.

RESULTS

Baseline characteristics of MARS-treated patients

Our study population consisted of 113 patients with ALF, 62 with AOCLF, 11 with GF, and six with miscellaneous liver failure (Figure 1). In total, 192 MARS treatment cases were included in this study. Four patients were treated before LTX and afterwards because of graft failure. These treatment sessions were categorized separately as individual cases, first according to the primary liver failure etiology, and later on as graft failure cases. In 30% (58/192) of all treated cases, alcohol was either partly (mixed intoxication, *n* = 13) or directly (chronic alcoholic-liver disease, *n* = 45; graft failure caused by alcohol, *n* = 1) related to liver failure. The median number of MARS treatments per patient was two (range: 1-13), and the median duration of one session was 16.5 h (range 4-22.5 h). Contraindications to LTX prior to MARS treatment were present in 35% (67/192) of cases and included substance abuse, serious psychiatric illness, patient decision, serious concomitant disease (e.g.

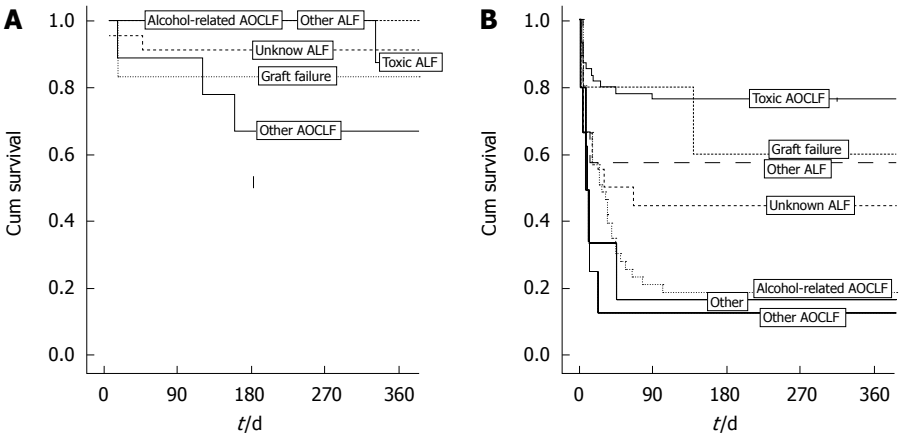

Figure 2 Kaplan-Meier cumulative survival for transplanted (A) and non-transplanted (B) MARS-treated patients with different causes of liver failure.

malignancy), and age > 80 years. In addition, 18 patients became untransplantable during MARS treatment: six because of serious, uncontrollable infections, and 12 because of multiorgan failure or brain death.

Etiologic subgroups differed significantly at baseline with respect to demographic data, clinical condition, and severity of liver failure (Table 2). The percentage of patients who required vasoactive medication and those with renal insufficiency were higher in the AOCLF and GF than in the ALF group. The highest median MELD scores were observed in association with alcohol-related AOCLF (39; range 17-52) and the lowest in association with ALF caused by toxicity (27; range 5-48) and GF (26; range 20-47) (Table 2). Encephalopathy grade decreased significantly in most subgroups during treatment. Changes in laboratory values during MARS treatment are presented in Table 3.

Outcome and characteristics of the subgroups

Kaplan-Meier 1-year survival curves for MARS-treated transplanted and non-transplanted patients are presented in Figure 2. The 1-year survival rate of all transplanted patients was 86% (43/50).

Patients with ALF: Patients with ALF were categorized into three subgroups according to etiology: toxic, unknown, and other (Figure 1). The toxic ALF subgroup was further subdivided into paracetamol-related and non-paracetamol-related intoxication caused by other drugs and toxins (e.g. *Amanita phalloides* or herbal products). The "other ALF" subgroup included patients with pregnancy-related ALF, Budd-Chiari syndrome, acute seropositive hepatitis, and hepatic trauma. A detailed analysis of the outcomes in these patients with ALF can be found in our previous study[18].

The 1-year overall survival rate of all ALF patients was 74% (84/113). The 1-year survival of transplanted ALF patients was 91% (30/33). The percentage of transplanted patients was 3% (1/32) of those with paracetamol-related ALF, 23% (7/31) of those with non-paracetamol-related ALF, 56% (23/41) of those with unknown-etiology ALF, and 22% (2/9) of those with other-etiology ALF. One-year survival rates of the transplanted and non-transplanted patients are shown in Figure 2. Six ALF patients died while waiting for a suitable graft. Half of these patients were non-encephalopathic at the initiation of MARS treatment.

Patients with AOCLF : All AOCLF patients were Child-Pugh class C and had a median MELD score of 36 (range 17-52). In 24% (11/45) of alcohol-related AOCLF and 12% (2/17) of other-etiology AOCLF patients, the liver was still enlarged and showed signs of steatosis.

In the alcohol-related AOCLF group, two abstinent patients received transplants. In other-etiology AOCLF, nine patients received transplants. The 1-year survival rates of non-transplanted and transplanted patients were, respectively, 19% (8/34) and 100% (2/2) in alcohol-related AOCLF, and 13% (1/8) and 67% (6/9) in other-etiology AOCLF.

In the alcohol-related AOCLF subgroup, the 1-year survival rate in non-transplanted patients with enlarged livers and signs of steatosis was significantly higher than in the other patients [55% (6/11) *vs* 6% (2/32); $P = 0.002$]. Both of these groups were comparable at baseline. The median MELD scores were 35 (range 24-48) in those with enlarged livers and steatosis and 39 (range 17-52) in the other patients.

Graft failure patients: In GF patients, 1-year survival rate was 73% (8/11). Four patients with early GF and two with late GF underwent retransplantation. The 1-year survival rates of non-retransplanted and retransplanted patients were, respectively, 50% (2/4) and 75% (3/4) in early GF, and 100% (1/1) and 100% (2/2) in late GF.

Miscellaneous etiology patients: All six patients in the subgroup with miscellaneous-etiology AOCLF had a contraindication to LTX. Only one patient with acute pancreatitis and ALF survived 1 year, and all other patients died within 2 mo of ICU admission.

Prognostic factors predicting 6-mo survival

The etiology of liver failure was highly significant in predicting patient outcome ($P < 0.0001$). The alcohol-related AOCLF subgroup with contraindications to LTX had the highest percentage of non-surviving patients.

In survival analysis, groups were divided into two categories: (1) transplant-free survivors, and (2) non-survivors and transplant recipients. At baseline, within the

Table 4 Demographic data, clinical condition, and laboratory parameters before treatment in survivors and non-survivors treated with MARS

	ALF			AOCLF		
	Transplant-free survivors	Non-survivors and transplant recipients	*P*	Transplant-free survivors	Non-survivors and transplant recipients	*P*
Demographic and clinical data at baseline						
Number of patients (*n*)	54	59		9	53	
Age, years (range)	39 (14-81)	50 (19-71)	< 0.0001	52 (30-58)	52 (16-75)	NS
Sex, male % (*n*)	52 (28)	31 (18)	0.021	67 (6)	62 (33)	NS
BMI, kg/m^2	24 (16.9-39.7)	27 (17-40)	NS	32 (18-38)	26 (20-56)	NS
MARS sessions/patient	2 (1-5)	3 (1-12)	< 0.0001	1 (1-3)	2 (1-13)	NS
Mechanical ventilation used % (*n*)	20 (11)	44 (26)	0.007	33 (3)	32 (17)	NS
Vasoactive-medication used % (*n*)	28 (15)	34 (20)	NS	33 (3)	60 (32)	NS
Renal insufficiency % (*n*)	32 (17)	39 (23)	NS	56 (5)	66 (35)	NS
MELD score (range)	24 (5-48)	32 (7-50)	< 0.0001	28 (17-48)	37 (25-52)	0.08
Encephalopathy grade prior to treatment	0 (0-4)	3 (0-4)	< 0.0001	1 (0-4)	1 (0-4)	NS
Laboratory values at baseline						
Hemoglobin g/L	113 (78-170)	106 (74-160)	NS	106 (80-127)	99 (59-130)	NS
Leucocytes 10^9/L	8.3 (1-23.4)	9.1 (2.6-41)	0.045	9.7 (1.4-35.3)	15.5 (1.6-39.3)	NS
Platelets 10^9/L	146 (11-351)	130 (37-511)	NS	131 (69-383)	107 (15-508)	NS
CRP g/L	10 (5-331)	8 (5-153)	NS	28 (8-58)	35 (5-110)	NS
Creatinine μmol/L	77 (35-1318)	91 (36-567)	NS	128 (56-556)	210 (29-686)	NS
Urea mmol/L	5.2 (1.1-31.2)	7.8 (0.8-29.3)	NS	8.4 (2.3-39.6)	17.45 (1.8-56.5)	NS
NH_4-ion μmol/L	50 (8-512)	99 (24-389)	< 0.0001	66 (12-241)	75 (19-311)	NS
Bilirubin μmol/L	71 (4-761)	425 (8-694)	< 0.0001	455 (17-745)	514 (143-909)	NS
AST U/L	732 (15-24360)	497 (50-20900)	NS	214 (27-2030)	164 (31-4540)	NS
ALT U/L	1165 (11-12500)	708 (71-10890)	NS	69 (9-2904)	87 (10-897)	NS
γ-GT U/L	61 (8-503)	109.5 (20-2139)	0.013	230 (44-398)	109 (19-1086)	NS
FV %	51 (7-201)	31 (5-101)	0.012	65 (41-124)	48 (7-125)	0.028
AT3 %	52 (15-125)	27 (15-110)	< 0.0001	40 (15-100)	29.5 (13-88)	0.043
TT (%)	26 (6-80)	16 (6-49)	< 0.0001	26 (9-96)	21 (6-135)	NS
INR	2.3 (1.1-7.7)	3.2 (1.4-9.9)	< 0.0001	2 (1-4.3)	2.4 (1-8.5)	NS
Albumin g/L	29.9 (19.2-46.4)	24.8 (11.5-41.2)	< 0.0001	23.3 (13.6-31.8)	21.8 (14.7-32.7)	NS

ALF group, the non-survivors and transplant recipients differed significantly from the transplant-free survivors in several clinical and laboratory parameters, including MELD score and levels of bilirubin, ammonium ion, and coagulation factors (Table 4).

In the AOCLF group, transplant-free survivors compared with non-survivors and transplant recipients had similar baseline values, except coagulation factor V and antithrombin Ⅲ plasma levels differed significantly (Table 4).

Factors predictive of survival were tested separately using stepwise binary logistic regression analyses in each etiological subgroup. The unwanted or negative endpoint was defined as death within 6 mo or LTX. All demographic and clinical parameters and laboratory values before MARS treatment presented in Tables 2 and 3 were included in these analyses. Additionally, in the toxic etiology subgroup, the analysis of the causative drug or poison was taken into account as an independent prognostic factor.

In the paracetamol-related toxic ALF subgroup, the only significant predictor of survival was the grade of hepatic encephalopathy at the beginning of treatment (OR, 0.345; 95% CI, 0.154-0.774; $P = 0.001$). Based on the equation below, hepatic encephalopathy grades from 0 to 4 predicted the probability (p) of survival at 6 mo to be, respectively, 98%, 94%, 85%, 65% and 40%. The positive predictive and negative predictive values, and the overall predictive accuracy based on the equation and the data were 92%, 57% and 84%, respectively. The sensitivity and the specificity were 67% and 89%, respectively.

$p = 100 \times [1/(1 + e^{-(3.831\text{-HE}*1.064)})]$.

In the non-paracetamol-related toxic ALF subgroup, significant predictors of survival were thrombin time, (TT) (OR, 1.103; 95% CI, 1.000-1.217; $P = 0.049$), and hepatic encephalopathy grade at the beginning of treatment (OR 0.562; 95% CI, 0.305-1.035; $P = 0.064$). The predicted probability (p) of survival at 6 mo was approximated by inserting the patient's variables into the equation given below. For example, a TT of 21% and encephalopathy grade of 2 predicted a survival probability of 45%. The positive predictive and negative predictive values and the overall predictive accuracy based on the equation and the data were 76%, 79% and 77%, respectively. The sensitivity and the specificity were 73% and 81%, respectively.

$p = 100 \times [1/(1 + e^{-(1.120 + \text{TT}*0.098\text{-HE}*0.577)})]$.

In the unknown etiology ALF subgroup, significant predictive factors for survival were coagulation factor V levels (OR, 1.052; 95% CI, 1.007-1.099; $P = 0.02$) and alanine aminotransferase ALT plasma levels (OR, 1.001; 95% CI, 1.000-1.001; $P = 0.013$). The predicted probability (p) of survival at 6 mo was approximated by inserting the patient's ALT and factor V levels (FV) into the equation given below. For example, an ALT value of 550 U/L and FV value of 33% gave a 6-mo survival probability of 6.5%. The positive and negative predictive

values and the overall predictive accuracy based on the equation and the data were 60%, 86% and 83%, respectively. Referring to the data, the sensitivity and the specificity of the equation were 94% and 38%, respectively.

$p = 100 \times [1/(1 + e^{-(-4.894 + ALT*0.001 + FV*0.051)})]$.

We were unable to find significant predictive variables in other etiological subgroups.

DISCUSSION

To the best of our knowledge, the present study of 188 patients represents the largest number of MARS-treated patients with liver failure investigated thus far in a single treatment unit. This is also believed to be the first attempt to examine prognostic factors predicting survival in different etiological subgroups of MARS-treated patients with liver failure. Prognostic and treatment efficacy estimations are becoming increasingly more important in today's ICU management, as the number of patients and per-patient costs continue to increase. In 2001, when we began using MARS therapy, it was unclear which patients would benefit from the treatment. The only available data on MARS at the time were from a few small studies conducted on patients with AOCLF[19-24]. Therefore, data with the planned protocol were collected prospectively from every MARS-treated patient in our ICU.

In AOCLF, some randomized studies[5,6,8,22] and small case series of MARS-treated patients[25-27] have reported favorable effects. However, conflicting reports have also emerged[28]. In review articles, MARS has been considered an effective and safe treatment[29,30], although in an early meta-analysis, it did not significantly reduce mortality[31]. In contrast to these studies, ours did not reveal any beneficial effect of MARS treatment on the outcome of AOCLF, except as bridging therapy. One reason that might explain this difference is patient selection. Our criteria for initiation of MARS therapy included at least two of the following: hyperbilirubinemia, hepatorenal syndrome, and encephalopathy. In the aforementioned studies, enrolled patients were in better clinical condition prior to treatment, which makes a direct comparison of results challenging. Also, in most other studies, follow-up time was significantly shorter than 1 year.

In the present study, we found that in the subgroup of non-transplanted patients with alcohol-related AOCLF, Child-Pugh class C, and no signs of hepatic steatosis or enlargement, the mortality was very high (94%). This suggests that MARS treatment in these patients was not beneficial, as it did not seem to improve the final outcome. Recently, a study by Wolff *et al*[32] led to a similar conclusion. Considering the poor survival results in patients with alcohol-related AOCLF, one might argue that MARS treatment should have been commenced earlier in the course of the disease, to benefit the patient. The optimal timing of MARS treatment in AOCLF was, and still is, unknown and requires further investigation. As most of our patients with AOCLF had end-stage cirrhosis, the regenerative capacity of the native liver was probably non-existent and the benefit of MARS treatment was only in bridging the patient to LTX. Furthermore, we were able to find a subgroup of patients with alcohol-related AOCLF with significantly better survival: patients with enlarged livers and signs of steatosis seemed to benefit more from MARS treatment, and had a significantly higher transplantation-free survival rate, even though all other baseline laboratory and clinical values were similar to those in other cirrhotic patients.

The 1-year survival rate of all transplanted patients was high (86%) in our study. Particularly in transplanted patients with ALF, the overall 1-year survival rate of 91% was significantly higher than the 1-year survival rates of 67%-83% that have been reported by western transplantation registers[15,33,34] and studies[35,36] in the past decade. This finding might be attributable to the observed improvement in many clinical and laboratory parameters in patients with AOCLF or ALF during MARS treatment. Additionally, the grade of encephalopathy decreased significantly in most patients. The fact that these patients were, therefore, in better clinical condition prior to LTX might contribute to the high overall survival of transplanted patients. The favorable effect of MARS treatment on laboratory parameters, as we observed, has also been reported in many small, uncontrolled studies[26,27,37-44]. However, the improvement in laboratory values alone might be only temporary and does not necessarily predict a favorable outcome. However, as noted in other studies, MARS treatment also seems to stabilize the patient hemodynamically and prevent the worsening of encephalopathy[18,19,41,45,46], thus helping to bridge the patient successfully to LTX.

The main goal of our study was to identify prognostic factors that could predict survival and help in the selection of patients for MARS treatment. Based on our data, we built mathematical prediction models to estimate the 6-mo survival probability of MARS-treated patients. The most important factor for survival and spontaneous recovery was the etiology of the liver disease. In both toxic ALF subgroups, the grade of encephalopathy prior to MARS treatment was a prognostic factor, and in the subgroup of non-paracetamol-related ALF, coagulation factor levels were prognostic as well. In the subgroup of unknown-etiology ALF, ALT levels and coagulation factor V levels were prognostic, but surprisingly, encephalopathy grade was not. In other liver failure subgroups, we were unable to detect variables that would accurately predict survival. MELD score was not included in this analysis because the target of this study was not to compare outcomes to previously investigated prognostic criteria, such as early lactate[47], the Clichy criteria[48], and the King's College criteria[49] for non-MARS treated patients with ALF, and the Child-Pugh class[50,51] or MELD score[15,52-54] for patients with AOCLF.

Thrombin time and factor V activity level were significant predictive factors in patients with non-paracetamol-related and unknown-etiology ALF, respectively. These factors emerged as predictive despite the fact that, in our ICU, treatment is usually started with intensive replacement of coagulation factors, to enable

the safe placement of a large-bore dialysis catheter. At the measurement of all baseline laboratory variables, the replacement therapy had already been administered to most patients. Additionally, calculation of the MELD score necessitates the use of the international normalized ratio (INR), and therefore, most patients scored much lower than they would have without prior coagulative therapy. Our results concurred with previous studies that factor V level[48,55] and prothrombin time[49] are significant predictors of survival in patients with ALF. Also, in our predictive model for unknown-etiology ALF, high plasma levels of ALT (which is released into the bloodstream from injured hepatocytes) correlated with improved survival. High serum ALT levels might reflect the initial stage of acute liver injury. As the condition progresses, there is less liver tissue to be destroyed, and thus the ALT levels fall, and the liver's capacity for spontaneous recovery and the probability of transplantation-free survival diminish. The simultaneous plunge in factor V levels further reflects the declining synthetic capacity of the remaining liver mass.

In the present study, the grade of hepatic encephalopathy at the beginning of treatment was a predictive factor of survival in the toxic-etiology ALF subgroup. In these patients, treatment was initiated in the absence of encephalopathy if the patient had ingested a lethal amount of toxin, such as *Amanita* mushrooms. This early treatment might improve the prognosis of these patients. Still, despite ICU and MARS treatment, three originally non-encephalopathic patients with ALF died while waiting for a suitable graft. This finding further emphasizes the importance of early referral and prompt commencement of treatment in a specialized unit[56,57]. In previous studies with non-MARS-treated patients with ALF, encephalopathy grade[49] as well as other clinical, serological and physical variables have been reported as predictors of survival[48,49,55,58-62].

Yuan *et al*[63] have reported recently on a study of the prognostic factors for early (30-d) mortality in MARS-treated patients scheduled for LTX. The study included a heterogeneous group of 50 patients with liver failure regarded and analyzed as one group. In Yuan's study, 68% of patients were transplanted compared to 25% of our patients. The 30-d postoperative survival was 82% in transplanted and 50% in non-transplanted patients. These 30-d survival figures correspond remarkably well with our respective 1-year outcome results (86% survival for transplanted and 47% survival for non-transplanted patients). The prognostic factors that correlated with early postoperative mortality in Yuan's study were sequential organ failure (SOFA) score, creatinine, INR, tumor necrosis factor-α, and interleukin-10. Encephalopathy grade was not considered significant in this analysis[63].

One of the limitations of our study is that it represents a very specific population and distribution of patients with liver failure in Finland. As the etiological factors and causative agents behind ALF and AOCLF vary between countries, the applicability of our results to other scenarios is probably reduced. In addition, there is also a likely selection bias associated with the acceptance of patients with AOCLF for MARS treatment. In Finland, alcohol-related AOCLF is a fairly common condition; these patients are usually treated in basic medical wards and not referred to our unit because chronic alcohol abuse with diagnosed cirrhosis is usually considered a contraindication to ICU treatment. Furthermore, the specificity and especially sensitivity of our predictive models were far from optimal. Ideally, a good prognostic tool would accurately, easily and cheaply predict the patient's survival probability and the need for LTX in the very early stages of the disease. In the real world, however, prognostic calculations can never predict the fate of an individual patient with 100% accuracy, as there are always exceptions to the rule, special circumstances, and multiple factors that were not considered in the prognostic model. At best, such calculations can be used as aids and facilitators, but not as substitutes, for the physician's clinical assessment.

In conclusion, the present study showed that, despite ICU and MARS treatment, patients with AOCLF and end-stage cirrhosis do not seem to benefit from MARS treatment without the possibility of LTX. In patients with alcohol-related AOCLF, we now use MARS treatment only with those whose liver is still enlarged and steatotic, with recovery capacity. The grade of encephalopathy and levels of coagulation factors were not consistently significant prognostic factors in all liver failure groups treated with MARS.

COMMENTS

Background

Rapidly failing liver function is a medical emergency that carries a high risk of mortality. Molecular adsorbent recirculating system (MARS) treatment is an extracorporeal albumin dialysis apparatus that has been used in the treatment of liver failure to enable native liver regeneration or as a bridge to liver transplantation (LTX).

Research frontiers

The impact of MARS treatment on outcome as well as clinical and laboratory variables has been investigated widely in small non-randomized studies. However, prognostic factors predicting survival in MARS-treated patients have only been explored in one study so far. The current hotspot of the research is to determine which patient groups actually benefit from MARS treatment. Another interesting question is whether there are patient groups that do not gain from MARS and should not be treated.

Innovations and breakthroughs

The prognostic factors predicting survival in MARS-treated patients have only been explored in one previous study by Yuan *et al*. That study comprised 50 patients with a heterogeneous etiological background and a follow-up of 30 d. The present study contained 188 patients with a heterogeneous etiological distribution. However, prognostic factors were searched for with logistic regression analysis in each etiological subgroup independently. In addition the follow-up time was 1 year. In the present study, the etiology of liver failure was the most important predictor of survival. In acute liver failure (ALF) with toxic etiology (e.g. paracetamol), the grade of encephalopathy before MARS treatment was a significant prognostic factor. In ALF of unknown etiology, coagulation factor V and liver enzyme alanine aminotransferase levels were prognostic. According to the authors results, the MARS treatment of a cirrhotic patient with an acute-on-chronic liver failure (AOCLF) is not meaningful in terms of prognosis if the patient is not eligible for transplantation.

Applications

MARS treatment appears to be a safe and effective treatment in ALF patients and those chronic liver disease patients who are eligible for LTX.

Terminology

MARS is an extracorporeal albumin dialysis machine that removes water-

soluble and albumin-bound toxins from the patient's blood. ALF is defined as rapid deterioration of liver synthetic and metabolic function in a person with no previous liver disease. AOCLF is a condition in which a previously stable patient with chronic liver disease experiences a rapid deterioration of liver function caused by some triggering event (e.g. gastrointestinal bleeding, infection or ingestion of alcohol). Cirrhosis is a consequence and the histological hallmark of chronic liver disease. It is characterized by the replacement of normal liver cells by scar tissue and eventually it leads to liver failure. Hepatic encephalopathy is a potentially reversible neuropsychiatric disorder presenting as a decreased level of consciousness associated with liver failure

Peer review

This is a well-written paper which has high clinical relevance. This was a unique single-center study of a large population of patients with ALF or AOCLF.

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